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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/247,886	02/10/1999	JUHA PUNNONEN	18097-030200	8163

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/247,886	Punnonen et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 9, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-13, 17-23, and 51-64* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-13, 17-23, and 51-64* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 12-9-02 has been entered. Claims 2, 18, 22, 23, 51-53 and 64 have been amended. Claims 2-13, 17-23 and 51-64 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 18-23, 51-58 and 64 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: how to determine whether the recombinant cell-specific binding moiety polypeptide has enhanced ability to bind to the target cell, what is the control that is compared to determine enhanced ability to bind the target cell.

Applicants amended claims 18 and 51 to read on "compared to the ability of a binding moiety polypeptide encoded of (1) to bind to the target cell (amendment, p. 6, 7). This is not found persuasive because step (1) of claim 18 is to recombine at least first and second forms of at least one nucleic acid that encodes a binding moiety polypeptide of an enterotoxin to produce a library of recombinant nucleic acids. Step (1) of claim 18 is directed to using nucleic acids to establish a library but not a binding moiety polypeptide. Further, there are more than one and could have hundreds of different nucleic acids encoding binding moiety polypeptides of enterotoxin. It is unclear which binding moiety polypeptide is being compared to determine

enhanced ability to bind target cells. Similarly, the amended claim 51 fails to clarify the indefiniteness for the same reason as set forth above.

3. Claims 2-13 and 59-63 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MEP. § 2172.01. The omitted steps are: how to determine whether the recombinant cell-specific binding moiety has an ability to increase uptake or specificity of a genetic vaccine for a target cell, what is the control that is compared to determine the enhanced ability of said recombinant cell-specific binding moiety.

4. Claims 2-13 and 59-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Step (1) of claim 2 is vague and renders the claim indefinite. It is unclear how the polynucleotide encoding a nucleic acid binding domain is associated with the polynucleotide encoding a cell-specific ligand in the library of recombinant binding moiety-encoding nucleic acids. It is unclear whether the polynucleotide encoding a nucleic acid binding domain is covalently bound or fused to the polynucleotide encoding a cell-specific ligand or they are separate from each other.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2-13, 17-23 and 51-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 2-13, 17 and 59-63 are drawn to a method for obtaining a recombinant cell-specific binding moiety for an ability to increase uptake or specificity of a genetic vaccine for a target cell by creating a library of vectors from a library of recombinant binding moiety encoding nucleic acid that encodes nucleic acid binding domain and a cell specific ligand, wherein the vector comprises said recombinant binding moiety and a binding site for said DNA binding domain, and a composition comprising said recombinant binding moiety and a polynucleotide sequence expressing an antigen and comprising a binding site. Claims 18-23, 51-58 and 64 are drawn to a method for obtaining a recombinant cell-specific binding moiety for an ability to increase uptake or specificity of a genetic vaccine for a target cell by creating a library of vectors from a library of recombinant nucleic acid encoding a binding moiety of an enterotoxin, recovering the recombinant cell-specific binding moiety polypeptide from host cells and contacting said polypeptide with a cell surface receptor of a target cell, and determining enhanced ability of said polypeptide to bind to the target cell.

The specification only discloses prophetic examples for selection of bacteriophage-derived delivery vehicles having enhanced ability to enter target cells and animal models for screening genetic vaccine vector. The claims encompass expressing polynucleotides encoding nucleic acid binding domains and cell-specific ligands to form a vector binding moiety complex and to screen for a recombinant cell-specific binding moiety for its ability to increase uptake or specificity of a genetic vaccine vector *in vitro* or *in vivo*. The claims also encompass expressing polynucleotides encoding a binding moiety polypeptide of enterotoxin to form a recombinant cell-specific binding moiety polypeptide and to screen for a recombinant cell-specific binding moiety for its ability to increase uptake or specificity of a genetic vaccine vector *in vitro* or *in vivo*.

The specification fails to provide adequate guidance and evidence for how the polynucleotide encoding a nucleic acid binding domain is associated with the polynucleotide encoding a cell-specific ligand in the library of recombinant binding moiety-encoding nucleic acids. Does those two polynucleotides are fused together or they are on separate vectors? The specification fails to provide adequate guidance and evidence for how the expression products of those two polynucleotides would form a recombinant binding-moiety and how to use said recombinant binding moiety to bind to a vector and screen for recombinant cell-specific binding moiety and nucleic acid encoding said moiety having enhanced ability for uptake and binding to target cells *in vitro* and *in vivo*. The specification also fails to provide adequate guidance and evidence how the vector of the vector-binding moiety complex would get into the target cell for

screening the desired recombinant cell-specific binding moiety when the expressed nucleic acid binding domain and cell-specific ligand are expressed separately and are not associated with each other. A dissociated cell-specific ligand that is separate from the nucleic acid binding domain can not deliver vector having the binding site for nucleic acid binding domain to target cells *in vitro* or *in vivo*. Thus, one skilled in the art at the time of the invention would not know how to use the claimed method to produce a recombinant binding moiety comprising a nucleic acid binding domain and a cell specific ligand and having enhanced ability for uptake and binding to target cells *in vitro* and *in vivo*.

The claims read on gene transfer *in vivo* and recovery of expressed gene product *in vivo*. The specification fails to provide adequate guidance and evidence for how to obtain or screen a recombinant binding moiety, comprising a nucleic acid binding domain and a cell specific ligand, or a recombinant binding moiety polypeptide of enterotoxin having enhanced ability for uptake and binding to target cells *in vivo*. The biological environment *in vivo* is very different from the biological environment *in vitro*. The factors in *in vitro* environment were well controlled, such as the type of medium, the ingredients of the medium, the temperature of the medium and the type of the container used. However, there are various unknown bioactive factors that can not be controlled *in vivo* and these bioactive factors interact with each other and with various regulatory elements. It was known in the art that a gene which is expressed *in vitro* is not necessarily to be expressed *in vivo* in various cell types because the microenvironment *in vitro* is different from the microenvironment *in vivo*. Further, Eck et al., 1996 (Goodman & Gilman's The

Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene transfer *in vivo* (e.g. bridging pages 81-82). In addition, administration routes and type of target cells for gene expression also affect the expression of the nucleic acid binding domain and cell-specific ligand *in vivo*.

For the reasons discussed above, one skilled in the art at the time of the invention would have to engaged in undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.